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Description

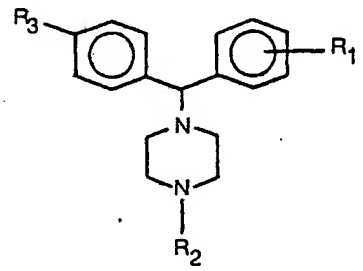
The present invention relates to new chemical compounds exhibiting antihistamine activity with low sedative potential.

US Patent 2,630,435 discloses a group of N-benzhydrylpiperazines with antihistamine activity, the most outstanding of which is the compound named 1-(4-Chlorobenzhydryl)-4-methylpiperazine and hereinafter referred to by its generic name, chlorcyclizine. Chlorcyclizine has gained a fair degree of clinical acceptance. However, like all other potent antihistamines in clinical use it produces sedation and drowsiness in varying degrees in most patients (L. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics,* 4th ed., p. 640, Macmillan, New York, 1970). This sedating effect limits the use of antihistamines by patients who must operate machinery, drive motor vehicles or must engage in activities requiring mental alertness.

AT—B—177 779 discloses asymmetrically substituted piperazine derivatives in which one of the nitrogen atoms is substituted with a benzyl group and the other is substituted with a benzhydryl group. The compounds are said to be antihistamines with low toxicity and an increased period of action. Each of the benzene rings may be unsubstituted or substituted with a halogen atom or alkyl or alkoxy groups.

A novel group of compounds having potent antihistamine activity which are substantially free from sedative effects, and which will have little or no anticholinergic effect has now been discovered.

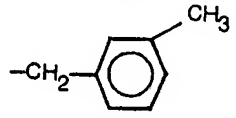
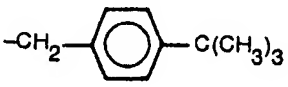
Accordingly this invention provides the compounds of formula I.



(I)

wherein R_1 is —COOH, —CH=CH—COOH, —$(CH_2)_n$COOH, or —O—$(CH_2)_n$COOH (n = 1 to 4). R_2 is alkyl (1-4 carbons) or benzyl which may bear alkyl substituents of 1-4 carbons. R_3 is alkoxy (1-4 carbons), alkyl (1-4 carbons), or halogen. This invention also includes ester and amide derivatives as well as acid addition salts and salts of the carboxylic acid group the compounds of formula (I).

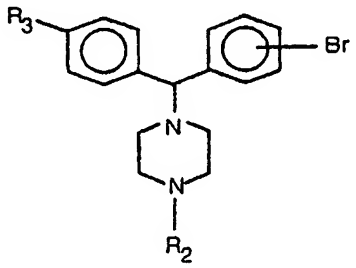
The compounds of formula (I) which were found to be particularly active are:

Compound	Example No.	R_1	R_2	R_3
A	1	3,-CH=CH—CO_2H	CH_3	—Cl
B	2	3,-COOH	—CH_3	—Cl
C	3	2,-COOH	—CH_3	—Cl
D	4	4,-COOH	—CH_3	—Cl
E	5	3-COOH	—CH_3	—OCH_3
F	6	3-OCH_2COOH	—CH_3	Cl
G	7	3-OCH_2COOH		Cl
H	8	3-OCH_2COOH		Cl

Compounds of formula (I) and their salts may be synthesized by methods known in the art for the synthesis of compounds having analogous structures.

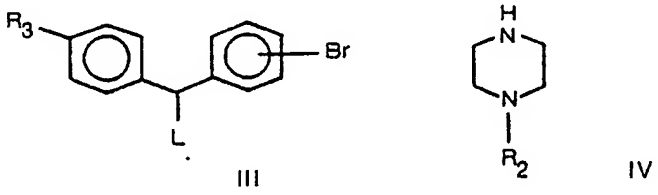
1. A method for preparing compounds of formula (I) when R_1 is —CH=CH—COOH (trans) comprises reacting a compound (II) in the presence of palladium with a protected form of acrylic acid such as an ester followed by deprotection of the acid group, e.g. hydrolysis.

Alternatively, compounds of formula (II) may be treated with n-butyllithium followed by dimethylformamide to give the corresponding benzaldehyde (IIa), which is then converted to compounds of formula (I) by the well-known Knoevenagel reaction with malonic acid or by Wittig reaction with an appropriate reagent such as $(C_2H_5O)_2POCH_2CO_2C_2H_5$, followed by basic hydrolysis.



(II)

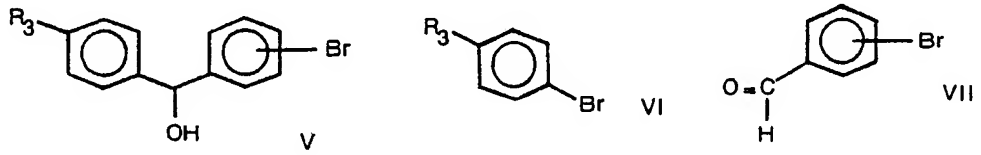
Compounds of formula (II) may be prepared by reacting a compound of formula (III) wherein L is a leaving group as defined by J. March, *Advanced Organic Chemistry,* 2nd ed., pp. 683 and 895, McGraw-Hill, New York, 1977, *e.g.* —Br, —Cl, toluene sulphonate, etc. with a piperazine (IV).



III IV

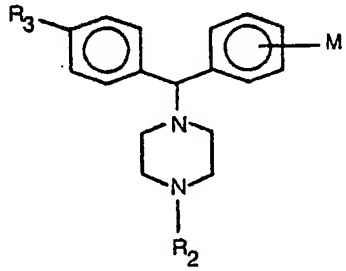
R_2 and R_3 are as defined above.

In turn compounds of formula (III) when L is Cl can be prepared by treatment of compounds of formula (V) with agents such as $SOCl_2$. Compounds of formula (V) can be obtained by reacting a compound of formula (VI) with n-butyllithium followed by condensation with the compound of formula (VII).



V VI VII

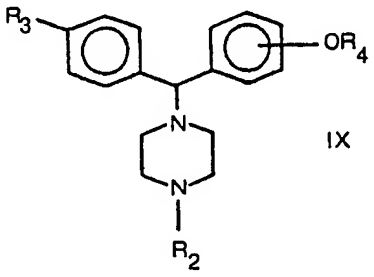
2. When the compounds of formula (I) have the carboxylic acid group directly on the phenyl ring preparation consists of reacting a compound of formula (II) with a suitable metallating reagent to produce a compound of formula (VIII) where M is an alkaline or alkaline earth metal.



VIII

For example n-butyllithium or magnesium with an appropriate solvent can be used to produce the lithium or magnesium (Grignard reagent) respectively. Compounds of formula (VIII) can be reacted with carbon dioxide to yield the corresponding compounds of formula (I).

3. Compounds of formula (I) when R_1 is $—O(CH_2)_nCOOH$ can be prepared by deprotecting compounds of formula (IX), (wherein R_4 is methyl, benzyl, or other suitable protecting group) by known methods, e.g. with boron tribromide where R_4 is methyl or benzyl, followed by base-catalyzed reaction of the resulting phenol (IXa) with compounds of formula (X), wherein L is defined as above and R_5 is lower alkyl or benzyl. The resulting ester may then be hydrolized to give the free acid.

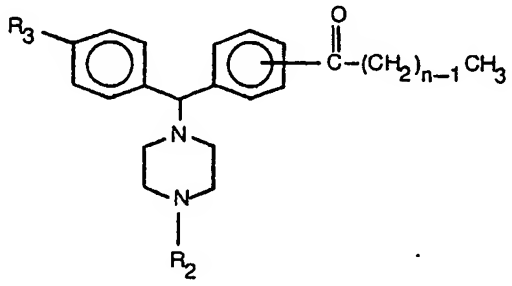


IX

$$L-(CH_2)_nCO_2R_5 \qquad X$$

Compounds of formula (IX) can be prepared by methods analogous to those used in the preparations of compounds of formula (II), with Br replaced throughout by $—OR_4$.

4. Compounds of formula (I) where R_1 is $—(CH_2)_nCOOH$ can be prepared from arylalkyl ketones of formula (XI) by application of the Willgerodt reaction (J. March, *op. cit.*, p. 1140) followed by hydrolysis of the resulting amide.



XI

Compounds of formula (XI) can be obtained from compounds of formula (II) by treatment with n-butyllithium followed by $CH_3(CH_2)_{n-1}CON(CH_3)_2$.

Alternatively, compounds of formula (I) where R_1 is $—(CH_2)_2COOH$ may be prepared by reduction, e.g. with hydrogen and platinum, of compounds of formula (I) where R_1 is $—CH=CHCOOH$.

Compounds of this invention have the same utilities as antihistamines used clinically at present. They may be used to relieve symptoms of nasal stuffiness due to colds and vasomotor rhinitis and for the symptomatic control of all allergic conditions including nasal allergy, perennial rhinitis, urticaria, angioneurotic oedema, allergic conjunctivitis, food allergy, drug and serum reactions, insect bites and stings and desensitizing reactions. The compounds are also indicated in all conditions responsive to its antipruritic activity including allergic dermatoses, neurodermatitis, anogenital pruritus, and pruritus of non-specific origin such as eczema, and of specific cause such as chickenpox, photosensitivity and sunburn. In contrast to the antihistamines in present use, the compounds of this invention are not sedating and have little or no anticholinergic side effects.

The amount of active compound required for use in the above conditions will vary both with the route of administration, the condition under treatment and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable oral dose of the active compound for a mammal is in the range of from 0.3 to 6.0 mg per kilogram body weight per day; preferably from 0.9 to 3.0 mg/kg. For example a typical dose for a human recipient of compound (A) is 2.1 mg/kg body weight per day.

The desired daily dose is preferably presented as from one to six sub-doses administered at appropriate intervals throughout the day as needed. Where three sub-doses of compounds of formula (I) are employed, each will preferably lie in the range of from 0.3 to 1.0 mg/kg body weight; for example, a typical sub-dose of compound for a human recipient is about 50 mg.

While it is possible for the active compound previously described to be administered alone as the raw chemical, it is preferable to present the active compound, a compound of formula (I), as a pharmaceutical formulation. Formulations of the present invention, both for veterinary and for human medical use, comprise the active compound together with one or more pharmaceutically acceptable carriers thereof and optionally any other therapeutic ingredients. For example, the active compound may be formulated with a sympathomimetic agent such as the decongestant pseudoephedrine, an antitussive such as codeine, an analgesic, an antiinflammatory, an antipyretic, or an expectorant. The carrier(s) must be pharmaceutically

acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, rectal, topical, nasal, ophthalmic or parenteral (including subcutaneous, intramuscular and intravenous) administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier or both and then, if necessary, shaping the product into the desired formulations.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound (defined herein as a compound of formula (I)); as a powder or granules; or a suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, with the active compound being in a free-flowing form such as a powder or granules which is optionally mixed with a binder, disintegrant, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets comprised of a mixture of the powdered active compound with any suitable carrier may be made by molding in a suitable machine.

A syrup may be made by adding the active compound to a concentrated, aqueous solution of a sugar for example sucrose to which may also be added any accessory ingredient(s). Such accessory ingredient(s) may include flavourings, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, such as a polyhydric alcohol for example, glycerol or sorbitol, and suitable preservatives.

Formulations for rectal administration may be presented as a suppository with a usual carrier such as cocoa butter, or hydrogenated fats or hydrogenated fatty carboxylic acids.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient.

Nasal spray formulations comprise purified aqueous solutions of the active compound with preservative agents and isotonic agents. Such formulations are adjusted to a pH and isotonic state compatible with the nasal mucous membranes.

Ophthalmic formulations are prepared by a similar method to the nasal spray except the pH and isotonic factors are adjusted to match that of the eye.

Topical formulations comprise the active compound dissolved or suspended in media such as mineral oil, petrolatum, polyhydroxy alcohols or other bases for topical pharmaceutical formulations. The addition of other accessory ingredients, *vide infra,* may be desirable.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavouring agents, binders, disintegrants, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

When used in medicine, the salts of the compound of formula (I) should be both pharmacologically and pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare the free active compound or pharmaceutically acceptable salts thereof and are not excluded from the scope of this invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, salicylic, toluene-*p*-sulphonic, tartaric, citric, methanesulphonic, formic, malonic, succinic, naphthalene-2-sulphonic and benzenesulphonic. Also pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group.

The following Examples are provided by the way of illustration of the present invention and should in no way be construed as a limitation thereof. All temperatures indicated are in degrees Celsius.

Example 1

(*E*)-3-(4-Chloro-α-(4-methyl-1-piperazinyl)-benzyl) cinnamic acid.

A solution of 4-bromochlorobenzene (20.0 g, 104 mmol) in 125 ml of dry tetrahydrofuran under nitrogen was cooled to −78° and 70 ml of 1.5M n-butyllithium in hexane was added dropwise over 20 minutes. After stirring another 10 minutes, 12.5 ml (104 mmol) of 3-bromobenzaldehyde was added dropwise and the reaction was stirred for another 10 minutes at −78°. Saturated aqueous ammonium chloride (100 ml) was added and the reaction was warmed to room temperature and extracted with 300 ml of ether. The ethereal layer was extracted with three 75 ml portions of 1M sodium bisulfite, 75 ml of 1M sodium hydroxide, 75 ml of water, and 75 ml of brine. The ether layer was dried over magnesium sulfate and the solvent removed to give 31.2 g of 3-bromo-4'-chlorobenzhydryl alcohol as a pale yellow solid. A portion was recrystallized from hexanes containing 5% ether to give white needles, m.p. 67—68°. Calc. for $C_{13}H_{10}BrCl$O: C, 52.47; H, 3.39; Br, 26.85; Cl, 11.91. Found: C, 52.25; H, 3.25; Br, 26.72; Cl, 12.09.

A solution of the above benzhydryl alcohol (13.0 g, 43 mmol) in 100 ml of methylene chloride and 5 mL of pyridine was stirred at room temperature during dropwise addition of 4.7 ml (64 mmol) of thionyl chloride in 20 mL of methylene chloride. After stirring overnight, the reaction solution was washed with two 60 mL portions of 1M hydrochloric acid and 50 mL of water and dried over magnesium sulfate. Evaporation of the solvent gave 14.0 g of 3-bromo-4'-chlorobenzhydryl chloride as a pale yellow oil. A portion was purified by chromatography on silica gel with hexane to give a colorless oil. Calc. for $C_{13}H_9BrCl_2$: C, 49.41; H, 2.87; Br, 25.28; Cl, 22.44. Found: C, 49.50; H, 2.82; Br, 25.27; Cl, 22.48.

The benzhydryl chloride from above (8.33 g, 26.4 mmol) in 10 ml of N-methylpiperazine was heated to 110° for 12 hours under nitrogen. After cooling to room temperature, the residue was dissolved in 75 ml of methylene chloride and washed with 40 mL of 1M sodium hydroxide and two 50 ml portions of water. After drying over sodium sulfate, the solvent was removed *in vacuo* to give 10.2 g of 1-(3-bromo-4'-chlorobenzhydryl)-4-methyl-piperazine as a dark oil. A portion of the oil was dissolved in ether and converted to the dihydrochloride salt with ethanolic hydrogen chloride. Recrystallization from 2:1 ethanol:methanol gave white powdery crystals, m.p. 229—231°. Calc. for $C_{18}H_{20}BrClN_2 \cdot 2HCl$: C, 47.76; H, 4.90; N, 6.19. Found: C, 47.55; H, 4.91; N, 6.13.

The benzhydrylpiperazine from above (1.12 g, 2.96 mmol) was dissolved in 6 ml of acetonitrile and placed in a 25 ml Teflon®-lined steel bomb with 0.53 mL (6.0 mmol) of methyl acrylate, 0.51 ml (3.7 mmol) of triethylamine, 17 mg (0.075 mmol) of palladium acetate, and 31 mg (0.12 mmol) of triphenylphosphine. The bomb was sealed and heated at 125° for 24 hours. The contents were dissolved in 20 ml of 1M hydrochloric acid and extracted with two 20 ml portions of ether. The acid layer was basified with 1M sodium hydroxide and extracted with 40 ml and 10 ml portions of chloroform. The combined chloroform extracts were dried over sodium sulfate and the solvent was removed to give 1.00 g of residue. Chromatography on silica gel (Waters Prep 500, methylene chloride containing 0.5% ethanol and 0.1% triethylamine) gave 433 mg (38%) of methyl (*E*)-3-(4-chloro-α-(4-methyl-1-piperazinyl)benzyl)cinnamate as a colorless oil.

The ester from above (1.05 g, 2.73 mmol) was dissolved in 20 ml of methanol with 8 ml of 1M potassium hydroxide and stirred overnight at room temperature. The methanol was removed *in vacuo* and the remaining aqueous solution was extracted with two 15 ml portions of ether. The aqueous layer was adjusted to a pH of 7 with 1M hydrochloric acid. The solution was chilled and the white powdery precipitate was collected by filtration to give 504 mg (46%) of (*E*)-3-(4-chloro-α-(4-methyl-1-piperazinyl)benzyl)-cinnamic acid, m.p. 131—141°. Calc. for $C_{21}H_{23}ClN_2O_2 \cdot 2H_2O$: C, 61.99; H, 6.69; N, 6.88; Cl, 8.71. Found: C, 61.98; H, 6.72; N, 6.89; Cl, 8.66.

Example 2

3-(4-Chloro-α-(4-methyl-1-piperazinyl)benzyl)benzoic acid.

The intermediate from Example 1, 1-(3-bromo-4'-chlorobenzhydryl)-4-methylpiperazine (1.10 g, 2.90 mmol), was dissolved in 10 ml of dry tetrahydrofuran and dried further over 4A molecular sieves for 24 hours. The solution was transferred to a dry flask under nitrogen and cooled to −78°. n-Butyllithium in hexane (1.1M, 2.6 ml) was added dropwise and the solution was stirred for 10 minutes at −78°. Carbon dioxide gas was bubbled into the reaction until the red solution turned yellow. The reaction was warmed to room temperature and the solvent was evaporated. The residue was dissolved in 20 ml of water and made basic with several drops of 1M sodium hydroxide. The aqueous solution was extracted with two 50 ml portions of ether and the pH was adjusted to 7—8 with 1M hydrochloric acid. After chilling in an ice bath, the precipitate was collected by filtration to give 341 mg (33%) of 3-(4-chloro-α-(4-methyl-1-piperazinyl)-benzyl)benzoic acid as a white powder, m.p. 225—230° (dec.). Calc. for $C_{19}H_{21}ClN_2O_2 \cdot 0.75\ H_2O$: C, 63.68; H, 6.33; N, 7.82; Cl, 9.89. Found: C, 63.68; H, 6.34; N, 7.82; Cl, 9.89.

The following Examples 3-5 were prepared by procedures similar to those used in obtaining Example 2.

Example 3

2-(4-Chloro-α-(4-methyl-1-piperazinyl)benzyl)benzoic acid.

Starting initially with 4-bromochlorobenzene and 2-bromobenzaldehyde, the final product was obtained as an off-white powder, m.p. 144—150°. Calc. for $C_{19}H_{21}ClN_2O_2 \cdot H_2O$: C, 62.89; H, 6.39; N, 7.72; Cl, 9.77. Found: C, 63.07; H, 6.03; N 7.79; Cl, 9.77.

Example 4

4-(4-Chloro-α-(4-methyl-1-piperazinyl)benzyl)benzoic acid.

Starting initially with 4-bromochlorobenzene and 4-brombenzaldehyde, the final product was obtained as an off-white powder, m.p. 250—255° (dec.). Calc. for $C_{19}H_{21}ClN_2O_2 \cdot 0.25\ H_2O$: C, 65.32; H, 6.20; N, 8.02; Cl, 10.15. Found: C, 65.23; H, 6.24; N, 8.02; Cl, 10.14.

Example 5

3-(4-Methoxy-α-(4-methyl-1-piperazinyl)benzyl)benzoic acid.

Starting initially with 4-bromoanisole and 3-bromobenzaldehyde, the final product was obtained as an impure solid which was converted to its oxalate salt and purified by crystallization from ethanol and ether

to give a pale yellow powder, m.p. 120—130° (dec.). Calc. for $C_{20}H_{24}N_2O_3 \cdot C_2H_2O_4 \cdot H_2O \cdot 0.5\ C_2H_5OH$: C, 58.59; H, 6.63; N, 5.94. Found: C, 58.23; H, 6.24; N, 5.86.

Example 6

3-(4-Chloro-α-(4-methyl-1-piperazinyl)benzyl)phenoxyacetic acid.

By the same method used in Example 1 for preparing 1-(3-bromo-4'-chlorobenzhydryl)-4-methylpiperazine, the preparation of 1-(3-benzyloxy-4'-chlorobenzhydryl)-4-methylpiperazine was accomplished starting with 4-bromochlorobenzene and 3-benzyloxybenzaldehyde. The final product was obtained as a white dihydrochloride salt, m.p. 168°—172°. Calc. for $C_{25}H_{27}ClN_2O \cdot 2HCl \cdot 0.75\ H_2O$: C, 60.86; H, 6.23; N, 5.68; Cl, 21.56. Found: C, 60.63; H, 5.94; N, 5.64; Cl, 21.40.

The dihydrochloride salt from above (12.0 g, 25 mmol) was suspended in 250 ml of methylene chloride and 50 ml of 0.5M boron tribromide in methylene chloride was added dropwise at room temperature. The reaction was stirred overnight and quenched by addition of 200 ml of methanol. The solvent was removed *in vacuo* and the residue was dissolved in 500 ml of water. After extraction with two 150 ml portions of ether, the aqueous layer was adjusted to a pH of 9 with 1M sodium hydroxide and extracted with four 200 ml portions of ether. The latter ether extract was dried over sodium sulfate and the solvent was removed to give 8.50 g of the resulting phenol, which was used without further purification.

A portion of the phenol (4.27 g, 13.5 mmol) was dissolved in 50 ml of dry tetrahydrofuran and added slowly to 650 mg (13.5 mmol) of 50% sodium hydride dispersion under nitrogen. The reaction was heated to reflux briefly to complete anion formation. After cooling to room temperature, 1.49 ml (13.5 mmol) of ethyl bromoacetate was added and the reaction was stirred for one hour. The reaction was diluted with 150 ml of ether and extracted with 90 ml of 0.3M hydrochloric acid. The aqueous layer was made basic with 1M sodium hydroxide and extracted with two 75 mL portions of ether. The extracts were dried over sodium sulfate and the solvent removed to give 3.98 g of ethyl 3-(4-chloro-α-(4-methyl-1-piperazinyl)benzyl)-phenoxyacetate as a yellow oil.

The ester from above (4.45 g, 11.0 mmol) was dissolved in 60 mL of methanol with 22 ml of 1M potassium hydroxide and stirred overnight at room temperature. The methanol was removed *in vacuo* and the remaining aqueous solution was diluted to 40 ml with water and extracted with 50 ml of ether. The aqueous solution was concentrated to 20 ml and 1M hydrochloric acid was added dropwise until precipitation occurred at a pH of 5. After settling for several hours, the supernatant was decanted from the oily yellow precipitate which was presumably the hydrochloride salt. Repeated attempts to crystallize this material were unsuccessful. The remaining product (1.8 g) was dissolved in 20 ml of 1M potassium hydroxide and the pH adjusted to 5 with 0.5M oxalic acid. The supernatant was decanted from the oily yellow precipitate, which was dissolved in 2:1 ethanol:methanol with excess oxalic acid and heat. Granular white crystals of the dioxalate salt formed upon cooling. A portion was recrystallized twice from 2:1 ethanol:methanol to give white prisms of 3-(4-chloro-α-(4-methyl-1-piperazinyl)benzyl)phenoxyacetic acid dioxalate, m.p. 173—175° (dec.). Calc. for $C_{20}H_{23}ClN_2O_3 \cdot 2\ C_2H_2O_4$: C, 48.42; H, 4.53; N, 4.34; Cl, 5.50. Found: C, 48.21; H, 4.57; N, 4.48; Cl, 5.73.

Example 7

3-(4-Chloro-α-(4-(3-methylbenzyl)-1-piperazinyl)benzyl)phenoxyacetic acid.

The ester ethyl 3-(4-chloro-α-(4-(3-methylbenzyl)-1-piperazinyl)benzyl)phenoxyacetate was prepared in a fashion analogous to the procedure of Example 6. The ester (4.8 g, 10 mmol) was dissolved in 90 ml of methanol with 10 ml of 4M potassium hydroxide. After stirring overnight at room temperature, the reaction solution was decanted from a small amount of gummy precipitate and evaporated to dryness. The residue was dissolved in chloroform and shaken with 50 ml of 1M hydrochloric acid, extracting the acid layer with a second portion of chloroform. The chloroform extracts were dried over magnesium sulfate and the solvent removed to give 5.1 g of beige foam. The product was crystallized from benzene containing a trace of ethanol to give 2.06 g of 3-(4-chloro-α-(4-(3-methylbenzyl)-1-piperazinyl)benzyl)phenoxyacetate acid as a hygroscopic white powder, m.p. 114—120°. Calc. for $C_{22}H_{24}ClN_2O_3 \cdot 0.3\ C_6H_6 \cdot 0.6\ H_2O$: C, 69.29; H, 6.46; N, 5.61; Cl, 7.10. Found: C, 69.30; H, 6.30; N, 5.43; Cl, 7.09.

Example 8

3-(4-Chloro-α-(4-(4-*tert*-butylbenzyl)-1-piperazinyl)benzyl)phenoxyacetic acid.

The title compound was prepared in the same way as Example 7 and was isolated as its hydrochloride salt by evaporating a solution in 5% isopropanol: benzene to give a hygroscopic white powder, m.p. 115—125° (dec.). Calc. for $C_{30}H_{35}ClN_2O_3 \cdot HCl \cdot 0.5\ C_6H_6 \cdot 0.75\ H_2O$: C, 66.49; H, 6.85; N, 4.70; Cl, 11.89. Found: C, 66.14; H, 6.47; N, 4.71; Cl, 11.62.

Example 9

Antihistaminic Activity

In vitro antihistaminic activity: The longitudinal muscle was isolated from the intact ileum of guinea-pigs (Hartley, male, 250—400 g) and placed in an organ bath under 300 mg tension. After one hour of equilibration, cumulative concentration-response curves (Van Rossum, J.M., *Arch. Int. Pharmacodyn. Ther. 143,* 299—330, 1963) to histamine were obtained. Following washing, the tissues were incubated for one

hour with the test compound and then a second histamine concentration-response curve was run. Antihistaminic activity was determined as pA_2 values by the method of Arunlakshana, O. and Schild, H.O. (*Br. J. Pharmacol: 14,* 48—58, 1959).

TABLE I

Results of Antihistamine Assays

Compound	pA_2*
Chlorcyclizine	8.6**
A	6.3
B	6.4
C	5.6
D	5.6
E	6.5
F	6.8
G	8.8
H	8.2

*Denotes the negative log of the concentration which gives a significant antihistaminic effect (higher pA_2 values indicate more potent antihistaminic activity).
**R.B. Barlow, Introduction to Chemical Pharmacology, *2nd* ed., p. 357, Wiley, New York, 1964.

Example 10

Formulations

(A)-Injection

Ingredient	Amount per ampoule
Compound of formula (I)	50.0 mg
Water for Injections, q.s.	1.0 ml

The finely ground active compound was dissolved in the water for Injections. The solution was filtered and sterilized by autoclaving.

(B)-Suppository

Ingredient	Amount per suppository
Compound of Formula (I)	50.0 mg
Cocoa Butter,	2.0 g
or Wecobee™ Base q.s.	

Wecobee is a trademark and is a hydrogenated fatty carboxylic acid.

The finely ground active compound was mixed with the melted suppository base (either Cocoa Butter or Wecobee™ base), poured into molds and allowed to cool to afford the desired suppositories.

(C)-syrup

Ingredient	Amount per 5 ml
Compound of Formula (I)	50.0 mg
Ethanol	0.3 mg
Sucrose	2.0 mg
Methylparaben	0.5 mg
Sodium Benzoate	0.5 mg
Cherry Flavour	q.s.
Coloring	q.s.
Water	q.s. to 5.0 ml

Ethanol, sucrose, sodium benzoate, methylparaben, and flavouring were combined in 70% of the total batch quantity of water. Coloring and the active compound were dissolved in the remaining water, then the two solutions were mixed and clarified by filtration.

(D)-Tablet

Ingredient	Amount per Tablet
Compound of Formula (I)	50.0 mg
Lactose	110.0 mg
Corn Starch, Pregelatinized	2.5 mg
Potato Starch	12.0 mg
Magnesium stearate	0.5 mg

The active compound was finely ground and intimately mixed with the powdered excipients lactose, corn starch, potato starch, and magnesium stearate. The formulation was then compressed to afford a tablet weighing 175 mg.

(E)-Capsule

Ingredient	Amount per Capsule
Compound of Formula (I)	50.0 mg
Lactose	440.0 mg
Magnesium Stearate	5.0

The finely ground active compound was mixed with the powdered excipients lactose, corn starch, and stearic acid and packed into gelatin capsules.

(F)-Tablet

Ingredient	Amount per Tablet
Compound of Formula (I)	50.0 mg
Pseudoephedrine HCl	60.0 mg
Lactose	62.5 mg
Potato Starch	14.0 mg
Magnesium Stearate	1.0 mg
Gelatin	2.8 mg

A tablet was prepared from the above formulation by the method previously described in Example 7 (D).

(G)-Syrup

Ingredient	Amount per 5 ml
Compound of Formula (I)	50.0 mg
Pseudoephedrine HCl	30.0 mg
Codeine Phosphate	10.0 mg
Guaifenesin	100 mg
Methylparaben	0.5 mg
Sodium benzoate	0.5 mg
Flavor	q.s.
Color	q.s.
Glycerol	500 mg
Sucrose	2000 mg
Purified Water	q.s. to 5.0 ml

A syrup containing other active ingredients in addition to a compound of formula (I) was prepared from the above ingredients by an analogous method to that described for Example 7 (C) above.

(H)-Nasal Spray

Ingredient	Amount per 100.0 ml
Compound of Formula (I)	5 g
Sodium Chloride	0.8 g
Preservative	0.5 g
Purified Water	q.s. 100.0 ml

The preservative was dissolved in warm purified water and after cooling to 25°—30°C the sodium chloride and the compound of formula (I) were added. The pH was then adjusted to 5.5—6.5 and purified water was added to bring the final volume to 100.0 ml.

(I)-Opthalmic Solution

Ingredient	Amount per 100.0 mL
Compound of Formula (I)	1.0 g
Sodium Chloride	0.8 g
Preservative	0.5 g
Water for Injection	q.s. 100.0 ml

This formulation was prepared in a similar way to the nasal spray.

(J)-Topical Cream

Ingredient	Amount per 100 g
Compound of Formula (I)	5.0 g
Emulsifying Wax, N.F.	15.0 g
Mineral Oil	5.0 g
White Petrolatum	5.0 g
Preservative	0.25 g
Purified Water	q.s. 100 g

The preservative was dissolved in approximately 50 g of warm purified water and after cooling to about 25°—30°C the compound of formula (I) was added. In a separate container the emulsifying wax, mineral oil, and white petrolatum were mixed well and heated to approximately 70°—80°C. The aqueous solution containing the compound of formula (I) was added to the warm mixture of emulsifying wax, mineral oil, and petrolatum with vigorous mixing while cooling to 25°C. Additional purified water was added with mixing to bring the total amount to 100.0 g.

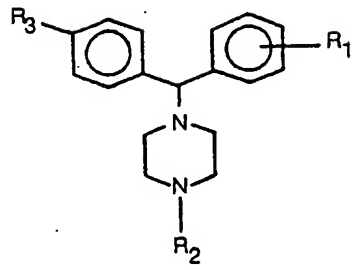
(K)-Topical Lotion

Ingredient	Amount per 100 ml
Compound of Formula (I)	50.0 g
Carbomer, N.F.	0.15 g
Triethanolamine	0.15 g
Preservative	0.5 g
Propyleneglycol	5.0 g
Purified Water	q.s. 100 ml

The preservative was dissolved in approximately 50 g of warm purified water and after this solution was cooled to 25°—30°C, the compound of formula (I) was added. The carbomer was mixed in next followed by triethanolamine and propyleneglycol. Purified water was added to bring the total amount to 100 ml and the formulation was mixed well.

Claims

1. A compound of formula (I):



(I)

or a salt, ester or amide thereof, wherein R_1 is —COOH, —CH=CH—COOH, —$(CH_2)_n$COOH, or —O—$(CH_2)_n$COOH (n = 1 to 4); R_2 is alkyl (1-4 carbons) or benzyl which may bear alkyl substituents of 1-4 carbons; R_3 is alkoxy (1-4 carbons), alkyl (1-4 carbons), or halogen.

2. A compound according to claim 1, or a salt, ester or amide thereof, wherein R_2 is methyl, methylbenzyl or t-butylbenzyl and R_3 is chloro or methoxy.

3. A compound selected from the group comprising:
(*E*)-3-(4-chloro-α-(4-methyl-1-piperazinyl)benzyl)-cinnamic acid;
3-(4-chloro-2-(4-methyl-1-piperazinyl)benzyl)benzoic acid;
2-(4-chloro-α-(4-methyl-1-piperazinyl)benzyl)benzoic acid;
4-(4-chloro-α-(4-methyl-1-piperazinyl)benzyl)benzoic acid;
3-(4-methoxy-α-(4-methyl-1-piperazinyl)benzyl)benzoic acid;
3-(4-chloro-α-(4-methyl-1-piperazinyl)benzyl)phenoxyacetic acid;
3-(4-chloro-α-(4-(3-methylbenzyl)-1-piperazinyl)benzyl)phenoxyacetic acid;
3-(4-chloro-α-(4-(4-*tert*-butylbenzyl)-1-piperazinyl)benzyl phenoxyacetic acid;
and the methyl ester of (*E*)-3-(4-chloro-α-(4-methyl-1-piperazinyl)benzyl-cinnamic acid.

4. A compound as claimed in any one of claims 1-3 for use in the treatment of nasal stuffiness due to colds and vasomotor rhinitis.

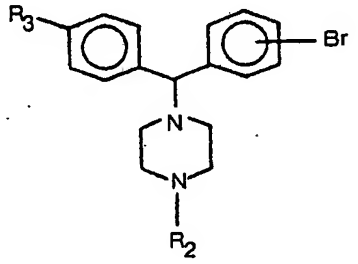
5. A compound as claimed in any one of claims 1-3 for use in the symptomatic control of allergic conditions.

6. A pharmaceutical formulation comprising a compound of the formula (I) as defined in claim 1 together with one or more pharmaceutically acceptable carriers and optionally any other therapeutic ingredients.

7. A method for the preparation of compounds of the formula (I) as defined in claim 1, which method comprises:

a) when it is desired to prepare compounds of formula (I) wherein R_1 is —CH=CH—CO_2H;

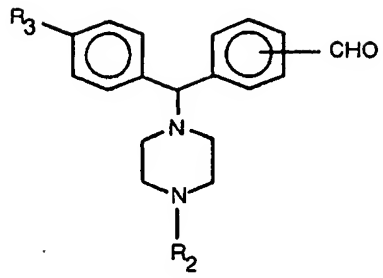
i) the reaction of a compound of the formula (II):



(II)

wherein R_2 and R_3 are as hereinbefore defined, in the presence of palladium with a protected form of acrylic acid, such as an ester, followed by deprotection of the acid group;

ii) the reaction of a compound of the formula (IIa):

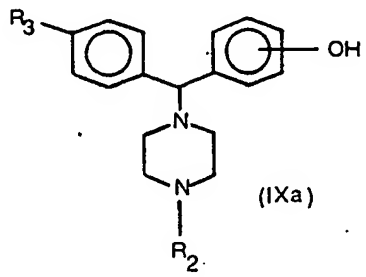


(IIa)

wherein R_2 and R_3 are as hereinbefore defined, with malonic acid or a Wittig reagent of the formula $R^x{}_3POCHCO_2R^y$, wherein R^x is phenyl or C_{1-4} alkyl and R^y is C_{1-4} alkyl, followed by basic hydrolysis;

b) when it is desired to prepare a compound of the formula (I) wherein R_1 is $—CO_2H$, the metallation of a compound of the formula (II) followed by reaction with carbon dioxide;

c) when it is desired to prepare a compound of the formula (I) wherein R_1 is $—O(CH_2)_nCO_2H$, the reaction of a compound of the formula (IXa), wherein R_2 and R_3 are as herebefore defined, with a compound of the formula (X) wherein L is a leaving group and R_5 is C_{1-4} alkyl or benzyl; or



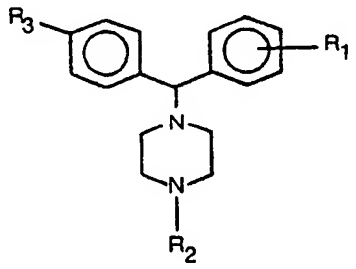
(IXa)

$$L—(CH_2)_nCO_2R_5 \qquad X$$

d) the conversion of one compound of the formula (I) into another compound of the formula (I) by the esterification of or formation of an amide from, a carboxylic acid; or the reduction of compounds of the formula (I) wherein R_1 is $CH=CHCO_2H$ to compounds of the formula (I) wherein R_1 is $CH_2CH_2CO_2H$.

Patentansprüche

1. Verbindung der Formel (I):



(I)

oder ein Salz, Ester oder Amid davon, worin R_1 —COOH, —CH=CH—COOH, $—(CH_2)_nCOOH$, oder $—O—(CH_2)_nCOOH$ (n = 1 bis 4) bedeutet; R_2 Alkyl(1-4 Kohlenstoffatome) oder Benzyl bedeutet, wobei Alkylsubstituenten mit 1-4 Kohlenstoffatomen enthalten sein können; R_3 Alkoxy(1-4 Kohlenstoffatome), Alkyl(1-4 Kohlenstoffatome) oder Halogen bedeutet.

2. Verbindung nach Anspruch 1 oder ein Salz, Ester oder Amid davon, worin R_2 Methyl, Methylbenzyl oder tert.-Butylbenzyl bedeutet und R_3 Chlor oder Methoxy ist.

3. Verbindung ausgewählt aus der Gruppe, enthaltend:
(E)-3-(4-Chlor-α-(4-methyl-1-piperazinyl)benzyl)-zimtsäure;
3-(4-Chlor-2-(4-methyl-1-piperazinyl)benzyl)-benzoesäure;
2-(4-Chlor-α-(4-methyl-1-piperazinyl)benzyl)-benzoesäure;
4-(4-Chlor-α-(4-methyl-1-piperazinyl)benzyl)-benzoesäure;
3-(4-Methoxy-α-(4-methyl-1-piperazinyl)benzyl)-benzoesäure;
3-(4-Chlor-α-(4-methyl-1-piperazinyl)benzyl)-phenoxyessigsäure;

3-(4-Chlor-α-(4-(3-methylbenzyl)-1-piperazinyl)benzyl-phenoxyessigsäure;

3-(4-Chlor-α-(4-(4-tert.butylbenzyl)-1-piperazinyl)benzylphenoxyessigsäure und der Methylester von (E)-3-(4-Chlor-α-(4-methyl-1-piperazinyl)benzyl-zimtsäure.

4. Verbindung nach einem der Ansprüche 1 bis 3 zur Verwendung in der Behandlung einer Nasenverstopfung aufgrund einer Erkältung und vasomotorischer Rhinitis.

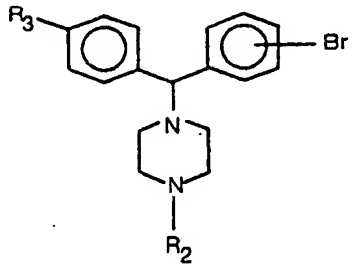
5. Verbindung nach einem der Ansprüche 1 bis 3 zur Verwendung in der symptomatischen Steuerung von allergischen Zuständen.

6. Pharmazeutische Formulierung, enthaltend eine Verbindung der Formel (I), wie in Anspruch 1 definiert, zusammen mit einem oder mehreren pharmazeutisch annehmbaren Trägerstoffen und ggf. anderen therapeutisch aktiven Bestandteilen.

7. Verfahren zur Herstellung von Verbindungen der Formel (I), wie in Anspruch 1 definiert, bei dem man:

a) wenn es erwünscht ist, eine Verbindung der Formel (I) herzustellen, worin R_1 —CH=CH—CO_2H bedeutet;

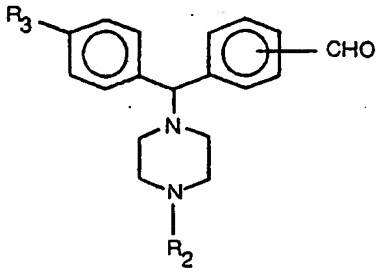
i) eine Verbindung der Formel (II):



(II)

worin R_2 und R_3 die vorhin gegebene Bedeutung aufweisen, in Gegenwart von Palladium mit einer geschützten Form von Acrylsäure, wie einem Ester, umsetzt, gefolgt von der Schutzentfernung der Säuregruppe;

(ii) einer Verbindung der Formel (IIa):

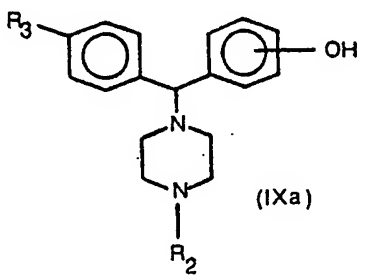


(IIa)

worin R_2 und R_3 die vorhin gegebene Bedeutung aufweisen, mit Malonsäure oder einem Wittig-Reagenz der Formel $R^x{}_3POCHCO_2R^y$, worin R^x Phenyl oder C_{1-4}-Alkyl und R^y C_{1-4}-Alkyl bedeutet, umsetzt, gefolgt von einer basischen Hydrolyse;

b) wenn es erwünscht ist, eine Verbindung der Formel (I) herzustellen, worin R_1 —CO_2H bedeutet, eine Verbindung der Formel (II) metalliert, gefolgt von einer Reaktion mit Kohlenstoffdioxid;

c) wenn es erwünscht ist, eine Verbindung der Formel (I) herzustellen, worin R_1 —$O(CH_2)_nCO_2H$ bedeutet, eine Verbindung der Formel (IXa), worin R_2 und R_3 die vorhin gegebene Bedeutung aufweisen, mit einer Verbindung der Formel (X), worin L eine austretende Gruppe und R_5 C_{1-4}-Alkyl oder Benzyl bedeutet, umsetzt;



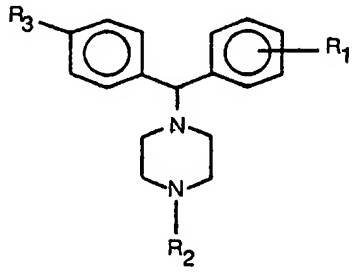
(IXa)

L—$(CH_2)_nCO_2R_5$ X

d) eine Verbindung der Formel (I) in eine andere Verbindung der Formel (I) durch Veresterung oder Bildung eines Amids, einer Carbonsäure überführt; oder die Verbindungen der Formel (I), worin R_1 $CH=CHCO_2H$ bedeutet zu Verbindungen der Formel (I), worin R_1 $CH_2CH_2CO_2H$ bedeutet, reduziert.

Revendications

1. Un composé de formule (I):



(I)

dans laquelle R_1 est —COOH, —CH=CH—COOH, $—(CH_2)_nCOOH$ ou $—O—(CH_2)_nCOOH$ (n = 1 à 4); R_2 est un groupe alkyle (1-4 atomes de carbone) ou benzyle qui peut porter des substituants alkyle de 1-4 atomes de carbone; et R_3 est un groupe alcoxy (1-4 atomes de carbone) ou alkyle (1-4 atomes de carbone) ou un halogène,
ou un sel, ester ou amide de ce composé.

2. Un composé selon la revendication 1, ou un sel, ester ou amide de ce composé, dans lequel R_2 est un groupe méthyle, méthylbenzyle ou t-butylbenzyle et R_3 est un groupe chloro ou méthoxy.

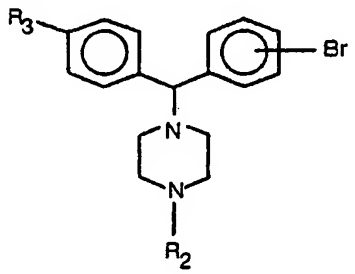
3. Un composé choisi dans le groupe formé par:
l'acide (*E*)-3-(4-chloro-α-(4-méthyl-1-pipérazinyl)benzyl)-cinnamique;
l'acide 3-(4-chloro-2-(4-méthyl-1-pipérazinyl)benzyl)-benzoïque;
l'acide 2-(4-chloro-α-(4-méthyl-1-pipérazinyl)benzyl)-benzoïque;
l'acide 4-(4-chloro-α-(4-méthyl-1-pipérazinyl)benzyl)-benzoïque;
l'acide 3-(4-méthoxy-α-(4-méthyl-1-pipérazinyl)benzyl)-benzoïque;
l'acide 3-(4-chloro-α-(4-méthyl-1-pipérazinyl)benzyl)-phénoxyacétique;
l'acide 3-(4-chloro-α-(4-(3-méthylbenzyl)-1-pipérazinyl)benzyl)phénoxyacétique;
l'acide 3-(4-chloro-α-(4-(4-tert.-butylbenzyl)-1-pipérazinyl)benzylphénoxyacétique; et
l'ester méthylique de l'acide (*E*)-3-(4-chloro-α-(4-méthyl-1-pipérazinyl)benzylcinnamique.

4. Un composé tel que revendiqué dans l'une quelconque des revendications 1-3, destiné à être utilisé dans le traitement d'un embarras de la respiration nasale dû aux rhumes et à la rhinite vasomotrice.

5. Un composé tel que revendiqué dans l'une quelconque des revendications 1-3, destiné à être utilisé dans la réduction symptomatique d'affections allergiques.

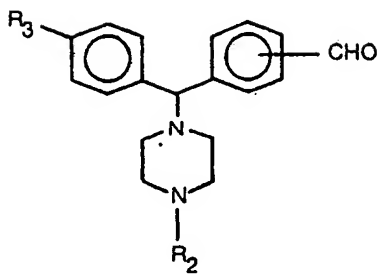
6. Une préparation pharmaceutique comprenant un composé de formule (I) comme défini dans la revendication l'ainsi qu'un ou plusieurs supports pharmaceutiquement acceptables et facultativement d'autres ingrédients thérapeutiques quelconques.

7. Un procédé pour la préparation de composés de formule (I) comme défini dans la revendication 1, lequel procédé comprend:
a) si l'on désire préparer des composés de formule (I) où R_1 est —CH=CH—CO_2H,
i) la réaction d'un composé de formule (II):



(II)

dans laquelle R_2 et R_3 sont comme définis précédemment, en présence de palladium avec de l'acide acrylique sous une forme protégée, telle qu'un ester, suivie par l'élimination de la protection du groupe acide;
ii) la réaction d'un composé de formule (IIa):

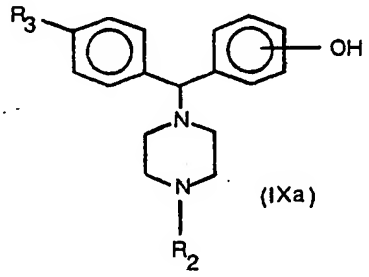


(IIa)

dans laquelle R_2 et R_3 sont comme définis précédemment, avec l'acide malonique ou un réactif de Wittig de formule $R^x{}_3POCHCO_2R^y$, dans laquelle R^x est un groupe phényle ou alkyle en C_1—C_4 et R^y est un groupe alkyle en C_1—C_4, suivie par une hydrolyse basique;

b) si l'on désire préparer un composé de formule (I) où R_1 est —CO_2H, l'introduction d'un atome de métal dans un composé de formule (II), suivie par une réaction avec l'anhydride carbonique;

c) si l'on désire préparer un composé de formule (I) où R_1 est —$O(CH_2)_nCO_2H$, la réaction d'un composé de formule (IXa), dans laquelle R_2 et R_3 sont comme définis précédemment, avec un composé de formule (X), dans laquelle L est un groupe partant et R_5 est un groupe alkyle en C_1—C_4 ou benzyle



(IXa)

$L-(CH_2)_nCO_2R_5$; ou X

d) la transformation d'un composé de formule (I) en un autre composé de formule (I) par estérification ou formation d'un amide à partir d'un acide carboxylique, ou la réduction de composés de formule (I) où R_1 est $CH=CHCO_2H$ en composés de formule (I) où R_1 est $CH_2CH_2CO_2H$.